

Advanced Product Development for Combat Casualty Care at the U.S. Army Institute of Surgical Research

**David G. Baer, Michael A Dubick, Joseph C. Wenke, CPT Laura L. McGhee,
Victor A. Convertino, COL Leopoldo C. Cancio, Steven E. Wolf,
COL Lorne H. Blackbourne**

U.S. Army Institute of Surgical Research
3400 Rawley E. Chambers Ave.
Fort Sam Houston, TX 78234
USA

David.G.Baer@us.army.mil, Michael.Dubick@us.army.mil, Joseph.Wenke@us.army.mil,
Laura.McGhee@us.army.mil, Victor.Convertino@us.army.mil, Lee.Cancio@us.army.mil,
steven.wolf@amedd.army.mil, Lorne.H.Blackbourne@us.army.mil

ABSTRACT

The Institute of Surgical Research (USAISR) is the U.S. Army's lead research laboratory for improving the care of combat casualties. The Institute follows a rigorous process for analyzing patterns of injury and the burden of disease to determine where research can be conducted in order to positively impact care. This analysis led the USAISR to focus research on: preventing death from bleeding; developing improved pain control techniques; developing improved vital signs analysis techniques; improving the treatment of extremity injuries; preventing burn injuries on the battlefield; and improving critical care for combat casualties. This process has resulted in numerous improvements in care on the battlefield. Highlights include development, fielding, and efficiency testing of tourniquets and improved dressings for bleeding control. Significant progress has also been made in the resuscitation of combat casualties using blood products instead of crystalloid or colloid solutions. Improvements in pain control include assessments of the effect of perioperative anesthetics on the development of Post-Traumatic Stress Disorder (PTSD). Novel vital signs analyses have been successful in identifying promising techniques which may improve the medic's ability to accurately triage patients. Current research in extremity injuries has focused on optimizing the use of negative pressure wound therapy for contaminated wounds. Burn research has focused on improving personnel protective equipment and developing continuous renal replacement therapy. This research program is soldier focused and addresses care from self aid and buddy aid through all echelons of care. Many of these advances have been adopted in civilian medical centers as well, benefiting not only the military trauma patient, but also the civilian trauma patient. The future of the USAISR includes expansion of the mission and resources to include dental, eye, and blood product research in collaboration with the U.S. Navy and U.S. Air Force as well as NATO partners.

1.0 RESEARCH PHILOSOPHY OF THE U.S. ARMY INSTITUTE OF SURGICAL RESEARCH

The United States military has been engaged in continuous operations since the fall of 2001, and thus has had ample opportunity to direct research and development efforts toward known patient populations from overseas contingency operations (OCOs). The responsibility to direct research at real-world problems is one that the US Army Institute of Surgical Research (USAISR) has pursued from the earliest days of the conflict, first in

Report Documentation Page		Form Approved OMB No. 0704-0188
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.		
1. REPORT DATE APR 2010	2. REPORT TYPE N/A	3. DATES COVERED -
4. TITLE AND SUBTITLE Advanced Product Development for Combat Casualty Care at the U.S. Army Institute of Surgical Research		5a. CONTRACT NUMBER
		5b. GRANT NUMBER
		5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER	
	5e. TASK NUMBER	
	5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Office of Naval Research Arlington, VA 22203 USA		8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)		10. SPONSOR/MONITOR'S ACRONYM(S)
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited		
13. SUPPLEMENTARY NOTES See also ADA564622. Use of Advanced Technologies and New Procedures in Medical Field Operations (Utilisation de technologies avancees et de procedures nouvelles dans les operations sanitaires). RTO-MP-HFM-182		
14. ABSTRACT The Institute of Surgical Research (USAISR) is the U.S. Armys lead research laboratory for improving the care of combat casualties. The Institute follows a rigorous process for analyzing patterns of injury and the burden of disease to determine where research can be conducted in order to positively impact care. This analysis led the USAISR to focus research on: preventing death from bleeding; developing improved pain control techniques; developing improved vital signs analysis techniques; improving the treatment of extremity injuries; preventing burn injuries on the battlefield; and improving critical care for combat casualties. This process has resulted in numerous improvements in care on the battlefield. Highlights include development, fielding, and efficiency testing of tourniquets and improved dressings for bleeding control. Significant progress has also been made in the resuscitation of combat casualties using blood products instead of crystalloid or colloid solutions. Improvements in pain control include assessments of the effect of perioperative anesthetics on the development of Post-Traumatic Stress Disorder (PTSD). Novel vital signs analyses have been successful in identifying promising techniques which may improve the medics ability to accurately triage patients. Current research in extremity injuries has focused on optimizing the use of negative pressure wound therapy for contaminated wounds. Burn research has focused on improving personnel protective equipment and developing continuous renal replacement therapy. This research program is soldier focused and addresses care from self aid and buddy aid through all echelons of care. Many of these advances have been adopted in civilian medical centers as well, benefiting not only the military trauma patient, but also the civilian trauma patient. The future of the USAISR includes expansion of the mission and resources to include dental, eye, and blood product research in collaboration with the U.S. Navy and U.S. Air Force as well as NATO partners.		

15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT SAR	18. NUMBER OF PAGES 12	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

the form of After Action Reviews, and then by more systematic methods , such as establishing databases and analysis capabilities to ensure that emerging injury patterns are identified and addressed. An important part of this analysis is the information provided by clinicians (physicians, physician assistants, nurses, and medics) who deploy to theaters of operations. Thus, we arrive at our paradigm for the conduct of research: battlefield medical issues are first identified, usually by deployed or returning health care providers, then they are investigated by using databases such as the Joint Theater Trauma Registry (JTTR) to determine the scope of the problem, and then research investment is made according to the scope of the problem. As the most important step to this process, research products, devices, drugs, techniques and practice guidelines are fielded to implement improvements to the care given to combat casualties. Finally, research is conducted to assess the changes in outcomes that result from changes in care.

2.0 MISSION SCOPE OF THE USAISR

The USAISR is a subordinate command of the US Army Medical Research and Materiel Command (USAMRMC). The MRMC has the broad mission to provide medical knowledge and materiel lifecycle management to protect, treat and optimize service member health and performance across the full spectrum of operations. As a part of this mission, the USAISR is focused on providing requirements driven combat casualty care medical solutions and products for injured soldiers from self-aid through definitive care, across the full spectrum of military operations. We share this mission of developing improved treatment for service members injured in combat with other organizations in the MRMC and thus focus our efforts in six major areas of emphasis:

- Damage Control Resuscitation
- Extremity Trauma and Regenerative Medicine
- Pain Control
- Advanced Capabilities for Emergency Medical Monitoring
- Critical Care Engineering
- Clinical Trials

These six areas, their accomplishments, and current research endeavors will be the focus of the remainder of this article.

3.0 DAMAGE CONTROL RESUSCITATION (DCR)

Hemorrhage remains the major cause of potentially preventable death on the battlefield in conventional warfare (12, 14). This fact has led the USAISR to invest significant efforts to improve the ability of soldiers to limit blood loss and treat hemorrhage at the point of injury. Accomplishments of this program include the fielding of safe and effective tourniquets and two generations of improved hemostatic dressings (15, 16). As a result of improved initial care, as well as rapid evacuation and positioning of surgical capabilities close to the point of injury, service members with severe injuries are surviving to reach field hospitals. This has resulted in lower overall mortality through a reduced Killed in Action (KIA) rate, but paradoxically, an increase in the Died of Wounds (DOW) rate. Reducing this rate is the current focus of much of the research in Damage Control Resuscitation (2). It is known that the severely injured may develop aspects of the lethal triad of acidosis, hypothermia and coagulopathy. Thus, the concept of DCR was developed as a structured intervention aimed to treat the approximately 8-10% of casualties who are the most severely injured, are

coagulopathic, and are at the greatest risk of dying. At USAISR, DCR combines research efforts in hemostasis and resuscitation to evaluate hemostatic dressings and to investigate optimal resuscitation strategies. Dilution of coagulation factors is avoided by using appropriate blood products (e.g., plasma) to provide these factors, oxygen carrying capability (RBCs), and sufficient volume to restore tissue perfusion and correct metabolism. Studies of severely injured patients have identified a population that appears to become hypocoagulable in response to trauma (as opposed to iatrogenic injury) (3). This phenomenon, termed the Acute Coagulopathy of Trauma (ACOT) is under investigation to determine its incidence, causes and potential treatments. The U.S. military has implemented the change from early resuscitation using crystalloid and packed red cells to early resuscitation using equal ratios of packed red cells, plasma, and platelets. Current research efforts attempt to refine this practice, optimize the use of blood products, and avoid delivering blood products to those that do not require this type of intervention. Other research efforts focus on identifying better means to treat non-compressible hemorrhage (17), as well as investigate genetic, genomic (18), and immunological (26) responses to trauma/hemorrhage and finding improved means to reduce hypothermia (9). Using relevant animal models and studies in human trauma patients, the ultimate goal is to develop products for resuscitation and hemorrhage control that can be used at all echelons of care to improve survival and reduce morbidity in injured Soldiers.

4.0 EXTREMITY TRAUMA AND REGENERATIVE MEDICINE

The majority of battlefield wounds occur to the extremities (55%) and head/neck region (30%) (24). Penetrating soft tissue wounds and open fractures account for the majority of the wounds in the extremities. Infection, delayed/nonunion, and impaired/loss of muscle function are common outcomes. The Extremity Trauma and Regenerative Medicine team is addressing these problems several different ways with the goal of returning the injured Warrior to full function.

First, injuries and their clinical outcomes are being defined. Until recently, there was not a good understanding of the injuries sustained by our Soldiers in ongoing conflicts. To help direct research efforts, retrospective studies were conducted to determine the incidence, rate, and qualitative outcomes of extremity injuries in the Iraq and Afghanistan conflicts (23). Currently, we are extending these studies and evaluating a database of over 200 type 3 open tibia fractures to determine what causes poor clinical outcomes (e.g., concomitant soft tissue loss, nerve defects, infection, type of fixation, etc.). We have also determined that skeletal muscle injury is the main reason for limited functional recovery (20) and are now directing resources to solve this problem. Perhaps most importantly, the Military Orthopaedic Trauma Registry (MOTR) was created. Currently, the JTTR does not collect the information that is needed to understand the severity of the extremity wounds, how they are treated, or their outcomes. MOTR will have these needed data elements.

Second, pre-clinical studies are conducted to determine which therapies have the greatest clinical potential. Various animal models that mimic traumatic injury are utilized to evaluate potential therapies for infection and soft tissue and bone injury. We strive to evaluate the most advanced and promising technologies using the most clinically relevant and stringent animal models possible. Clinical practice guidelines for irrigation of contaminated wounds have been created from studies that we conducted in animals (25, 34). Other notable efforts include developing animal models for compartment syndrome, massive contaminated defects, and large segmental muscle loss. The concept of a dual-purpose bone implant (promotes regeneration and prevents infection) was developed and is being evaluated. There is an active regenerative medicine program that has established the ability to use stem cells as a therapy for skin, muscle, and bone injuries while collaborations have made a wide variety of biomaterials readily available for evaluation in soft tissue and bone defects.

Third, we are initiating prospective clinical trials aimed at improving outcomes of extremity wounds. The Department of Orthopedics has initiated several clinical trials in the areas of combat casualty care and several more are planned in the near future. We have established multi-center clinical trials consortium through a cooperative agreement with Orthopaedic Extremity Trauma Research Program (OETRP). Capable military orthopaedic departments will be members of this consortium; this will further develop needed infrastructure, allow military personnel to gain expertise, and will solidify a research culture within these orthopaedic departments.

Finally, we are actively involved in extramural research programs. The USAISR manages the OETRP, and we are active partners in the Armed Forces Institute of Regenerative Medicine (AFIRM). The OETRP focuses on improving outcomes of extremity injuries within the next 5 years. This is accomplished by funding translational research projects that are evaluating new and emerging therapies and by conducting clinical trials to evaluate current standards of care and available treatments. AFIRM is a collaboration between military and civilian research consortia, focused on utilizing regenerative medicine to improve outcomes on injured warriors who have sustained extremity, craniomaxillofacial, and burn injuries. Most of the immediate clinical efforts from AFIRM will be in skin replacement and scar mitigation along with use of composite tissue allografts. In addition, the USAISR provides technical oversight to more than 20 large research contracts with universities and companies. These relationships are used to advance scientific inquiry in the areas of soft tissue and bone injury, infection, and tissue regeneration.

In summary, we have made great strides in identifying the clinical challenges to optimum functional outcomes and are addressing them in a systematic fashion. There is much work to be done in clinical trials to determine what available treatment options are most effective. This effort will allow us to establish a clinical research culture within the U.S. Department of Defense and a multi-center trial network within the civilian sector. Regenerative medicine therapies hold the key for complete recovery of severely injured warriors. These therapies are emerging but are not mature enough to make significant clinical improvements immediately. Pre-clinical work needs to be done to determine what approaches are most effective, and this work will serve as a pipeline for future clinical trials. Our goal in the immediate future is to continue to make improvements by determining what currently available therapies are best. As new and promising advances in regenerative medicine emerge, we will be ready and capable to implement them into the clinic with the goal of returning the injured warriors to full function.

5.0 PAIN CONTROL

Pain, both acute and chronic, is recognized as a leading problem among US soldiers injured on active duty or during deployments. Pain is experienced throughout the continuum of trauma care and within all ranks of the military. Recent initiatives have started tracking pain scores from as early as time of admission to the Emergency Department (ED) at Level 2 and Level 3 facilities. Of soldiers admitted to Level 2 and Level 3 facilities, 71% experience pain of 5 or greater on a scale of 0 to 10. Accepted clinical guidelines classify pain of 5 or greater as severe pain and recommend treating pain rated as 4 or greater. Despite the best efforts of clinicians, pain control remains elusive and is especially difficult in austere evacuation environments. In the Veterans Affairs Health System, pain is one of the most common complaints and often the reason for acute medical appointments. These patients often have multiple co-morbidities including PTSD, anxiety and depression. Recent evidence suggests that uncontrolled acute pain leads to neuronal remodeling and increased incidence of chronic pain. Chronic pain and PTSD are often co-morbid conditions in which a positive feedback cycle exacerbates the symptoms of each disease.

The over-arching goal of this research area is the study of pain from the battlefield through recovery. Particular attention is paid to identifying of novel pain control techniques (including novel pain control targets) and molecular mechanisms in the pain pathway. Focus is also placed on determining the effect of battlefield pain and pain control on short-term and long-term outcomes such as acute and chronic pain syndromes, the incidence of PTSD and psychopathological development (10), and the relationship of resuscitative fluid requirements to analgesic/anesthetic choices. The ultimate objective is to improve patient outcomes with better pain control methods.

Current research projects include studies which examine the effects of anesthetic agents on short-term outcomes such as resuscitation requirements and optimal transfusion ratios. Long-term outcomes such as PTSD, patient satisfaction (health care related quality of life), opioid addiction/tolerance, and chronic pain are also being studied. In a retrospective study, ketamine was not associated with an increased prevalence of PTSD and was correlated with decreased PTSD development in burned soldiers (22). These results were in contrast to concerns that ketamine, a psychoactive drug, would increase PTSD development. Later work showed that propranolol was not associated with a decrease in PTSD development in burned soldiers despite its effects on memory and occasional off-label use as a PTSD prophylactic (21).

Another area of effort is evaluation of the utility of Virtual Reality (VR) for acute pain control (31). Immersive VR is being studied as a means to decrease opioid requirements and improve pain control; all while decreasing NPO restrictions and increasing levels of alertness and active participation in subsequent daily rehabilitation sessions. Wounded Warriors enter the virtual world, known as Snow World, where icy landscapes of frigid tundra and frozen canyons are coupled with snowflakes, polar igloos and arctic animals designed to decrease the pain, anxiety and mental stress normally associated with daily burn wound dressing changes. Soldiers then interact with the virtual world via high resolution optics, noise cancelling headphones and a computer mouse which allows them to target and expel native or hostile opposition forces. Patients endorse improved pain control and overall satisfaction, and their families are also appreciative because of decreased sedation. While initially used for daily dressing changes on burned soldiers, plans are underway to incorporate this technology into daily physical/occupational therapy procedures to assist patients during painful rehabilitation sessions.

Other current projects include an evaluation of the utility of Ultra Rapid Opioid Detoxification under Anesthesia (URODA) in decreasing narcotic consumption and opioid dependence in burned soldiers. Within our burn center, increased and improved ketamine utilization was evident subsequent to development and implementation of a standardized electronic ketamine order set and guidelines. The research area also provided ongoing support for development of the intranasal ketamine product being fielded as a potential “silver-bullet” for battlefield pain control in the hands of combat medics. Current perioperative projects include using intravascular temperature management during severe burn surgery to minimize hypothermia and meet OSHA requirements for a safe workplace, evaluating high ratios of plasma:PRBC interoperative transfusions to reduce postoperative transfusion requirements, and the evaluation of a supraglottic airway device for prone position rescue airway management.

While the recognition of pain as a disease process rather than a symptom has shed light onto the important role of pain, a more comprehensive understanding of pain has yet to be achieved. In collaborations with Dr. Neal Smith and Lt Col Aldington (Anaesthetist and Pain Specialist, UK Armed Forces), we are investigating how to collect chronic pain data (in particular, the effects of early pharmacological and non-pharmacological interventions on long term outcomes) and how such data should be utilized to inform treatment regimes. Major hurdles include the unreliability of medical records when collected from austere environments with inherently limited access and availability, and the lack of consensus tools for validating pain research.

Although significant advancements have been made in the acute pain care of wounded soldiers, we are just beginning to realize the far-reaching impacts of suboptimal pain management on health processes; to include inflammation, immunosuppression, longer hospital stays with slower recovery times, less effective physical rehabilitation, neuropsychological pathology, and poor quality of life. As leaders in the management and research into pain control, military pain specialists have established themselves as indispensable members of the combat casualty team and the soldier's primary advocate in the treatment of pain. In the eternal words of Dr. John J. Bonica in *The Management of Pain*, "The proper management of pain remains, after all, the most important obligation, the main objective, and the crowning achievement of every physician."

6.0 ADVANCED CAPABILITIES FOR EMERGENCY MEDICAL MONITORING

The objective of the Advanced Capabilities for Emergency Medical Monitoring program is to conduct basic and applied research that leads to the identification and integration of physiological measures that reflect the complexity of compensatory responses during the early dynamic phase(s) of hemorrhage. The goal is to apply this knowledge to direct the development of new technologies and devices that advance the medical monitoring capabilities of combat medical personnel for triage, diagnosis and decision-making relative to combat casualty management. Basic research efforts focus on investigating the time course of central hemodynamics, autonomic functions, and peripheral tissue metabolism during progressive reductions in central blood volume induced by lower body negative pressure in healthy human subjects (6). Basic research efforts are also used to investigate and describe the physiological signals that distinguish patients with low tolerance (non-responders) to reductions in blood volume from those with high tolerance. Evolving technologies to be used to assess early and continuous alterations in central hemodynamics, autonomic functions and tissue perfusion include bioimpedance, real time measures of beat-to-beat and waveform analysis of arterial blood pressure for stroke volume estimates and pressure oscillations, direct measurement of sympathetic nerve activity (7), linear and non-linear frequency analysis of R-R interval captured from a standard ECG (heart rate variability indices to assess autonomic oscillations; heart rate complexity indices), and near infrared spectroscopy (muscle oxygenation, pH, lactate) (32, 33). Loss of coherence between blood pressure and sympathetic activity initiated by reaching a minimum threshold of cardiac filling will be investigated as a potential mechanism of hemodynamic decompensation during progressive reductions in central blood volume. The impact of other combat-related stressors such as heat, cold, exercise and anxiety on physiological measures associated with monitoring patients with hemorrhage will also be investigated.

Research includes studies designed to test and develop new 'wear-and-forget' Physiological Status Monitors (PSM) that enhance far forward capabilities for remote triage, diagnosis, and decision-making relative to casualty management. We continue the investigation of the applicability of information that can be obtained from the electrocardiogram and other sensor signals of the PSM to specifically track reduction in central blood volume resulting from hemorrhage, and further define the practical requirements (i.e., computing power, heart beats required, etc.) for their potential use on the battlefield (27). We also investigate technologies using light sources for the development of standoff triage. Emphasis is placed on developing a machine-learning algorithm that will provide early indication of severity of hemorrhage and subsequent need for prioritization of treatment or evacuation.

We are conducting research designed to develop and test new portable medical monitors that can be used by combat medical personnel during en route care and at higher echelons (e.g., ER). Current studies focus on identifying devices for vital sign monitoring, diagnostics and therapeutics for remote and on-scene assessment of the severity of hemorrhage and early prediction of onset of hemodynamic decompensation and progression toward the development of overt hemorrhagic shock. Technologies under consideration to meet these needs

include infrared photoplethysmography, near-infrared spectroscopy, diffuse optical spectroscopy (19), and inspiratory resistance (29). The ultimate goal is to integrate these measurements using machine-learning techniques to develop a predictive, personalized algorithm for triage. We will also initiate laboratory and field studies designed to test algorithms under conditions that might challenge their efficacy but which may be experienced by soldiers during combat (e.g., heat, cold, dehydration, exercise).

In addition to the emphasis placed on personalized prediction of impending hemorrhagic shock, we will use our experimental human algorithm for predicting central blood volume changes to focus on the development of software algorithms and systems to provide a capability to track, and subsequently guide, resuscitation efforts.

7.0 COMBAT CASUALTY CARE ENGINEERING

Combat Casualty Care Engineering is directed at improving care by responding to a Critical Care Technology Gap on the current battlefield, particularly at echelons 2 and higher and en route. This gap exists because it is difficult, given current technology levels, to provide the same state-of-the-art care on the battlefield as can be provided in a U.S. trauma center Emergency Department (ED) or Intensive Care Unit (ICU). This problem is magnified during inter-facility transport. In general, as a casualty moves to higher echelons of care, the resources available increase and care approaches the standards of a civilian or military hospital in the continental United States. This gap between the highest standard of care and that available at earlier echelons (and the even larger gap that exists as casualties are moved between facilities) is the target of research and development efforts in Combat Casualty Care Engineering.

The potential impact of improvements in critical care capabilities on mortality and on resource utilization was suggested by Grathwohl (11). In that study, both ICU length of stay, and ICU mortality, decreased progressively at the Combat Support Hospital in Baghdad as the model changed from No Intensivist, to Intensivist Consult, to Intensivist-Directed Team. Similar convincing results have been seen in U.S. hospitals. The problem, however, is the scarcity of such manpower on the battlefield: “Despite a rapidly mobile critical care platform, the U.S. military is unfortunately faced with... shortages of critical care physicians and nurses to staff extended worldwide missions.” The goal of Combat Casualty Care Engineering is to develop new systems-based technology which creatively fills this Critical Care gap. Technology in this sense means hardware and software systems which incorporate sensors, processors, and effectors and includes new vital signs, automated critical care, and better effectors.

Current vital signs used to diagnosis and treatment of trauma patients do not provide an accurate assessment of the true injury severity and are only useful after patient has decompensated. New vital signs will be explored that will provide personnel with more sensitive and specific indicators of the true extent of trauma injuries, in addition to providing more precise diagnosis at earlier stages of care. These new vital signs will allow for better and earlier diagnosis of impending cardiovascular collapse and will provide personnel with a more accurate indicator of the need for a life saving intervention. New vital signs will be developed through research into new approaches for processing current vital signs (1), research on data fusion and multivariate analysis approaches for processing combinations or groups of different vital signs simultaneously, and use of artificial intelligence technologies for learning vital sign patterns that can be used for prediction and diagnosis. Part of this research involves the user of high performance computing approaches for feature extraction of high frequency and high resolution waveform data digitized from different body sensors (i.e., EKG). Additionally, advanced information and computer processing approaches will be used to develop systems that can process and implement these new vital signs in smaller and lighter monitoring systems that can be carried by medics in the battlefield.

Automated critical care deals with developing new approaches that use information technology to help the care provider by reducing large volumes of data generated by the patient care environment into decision support systems, open-loop systems, and, eventually, full automated control of critical care processes (30). Decision support systems will be developed that push knowledge from the expert clinician to the non expert provider for many critical care procedures. By providing the user with sets of recommendations on procedures and treatments based on the knowledge from expert care providers and standards of care, patient treatments become more efficient, less variable, and result in better patient care. One example is the USAISR decision support system for burn resuscitation. This system has been successfully used to resuscitate patients with serious burns in the USAISR burn center with better outcomes compared to standard non computerized approaches. To further automate critical care procedures, open loop systems will also be developed that will provide personnel with recommendations on treatment options in addition to providing the ability to execute the intervention automatically. Finally, closed loop control systems will be developed to fully automate the care of the patient with little or no intervention from the provider.

Research into better effectors is currently focused on ventilator systems for support of patients in austere environments. The focus is on development of simplified ventilators that can be used in patients with severe traumatic brain injury (TBI), acute respiratory distress syndrome (ARDS), smoke inhalation injury, pulmonary contusions, and/or massive transfusion. Development of extracorporeal devices will be explored with capabilities to augment and/or replace mechanical ventilation requirements for patients with severe ARDS. This need is driven by the continued high mortality rate of trauma patients with ARDS which is approximately 30%. Research will be based on data and recommendations generated from the ARDSnet trial in addition to results from USAISR research protocols.

The core capabilities which the Combat Casualty Care Engineering program brings include an integrated team of intramural and extramural collaborators, consisting of combat-experienced trauma surgeons and intensivists; computer scientists; biomedical engineers; and physiologists. Because of the heavy emphasis on trauma patient validation and rapid product delivery to the battlefield, the focus of Combat Casualty Care Engineering is on clinical trials in trauma and burn patients, and on product testing in clinically relevant models of severe injury where appropriate.

8.0 CLINICAL TRIALS

The US Army institute of Surgical Research Clinical Trials program has two primary objectives within the Combat Casualty Care Research Program. The first is to observe current combat casualties to identify emergent challenges and opportunities for improved care. The USAISR serves as the only American Burn Association verified burn center in the Department of Defense, the USAISR receives all significant burn injured service members evacuated from the wars in Iraq and Afghanistan. As a result, we have the opportunity to observe patterns of injury and implement programs in order to prevent and better treat these burns. Examples include identification of significant numbers of waste burning accidents and implementation of an awareness program (13), identification of large numbers of debilitating hand burns and implementation of a rapid equipping program for fire resistant gloves (35), identification of thermal injury to the portions of the torso not covered by body armor and development of improved protective clothing, and identification of over resuscitation injury and implementation of a burn resuscitation flow sheet to ensure appropriate care. The second objective is to translate pre-clinical research from the other research areas at the institute into a clinical environment for validation. Examples of this type of translational effort include testing of wound care dressings in donor sites, and assessment of damage control resuscitation strategies in the burn operating room. The USAISR is unique within the Medical Research and Materiel Command in that we have both a clinical

population and research scientists working within the same laboratory. This collaborative, integrated research platform gives us the ability to translate science into improvements in combat casualty care and deliver these improvements to the battlefield.

The USAISR Clinical Research program prides itself on being responsive to clinical problems and striving for excellence in burn care, critical care medicine, and the care of the multiply injured casualty. Clinical research in injured casualties is being conducted on a variety of medical advances including resuscitation protocols and stabilization in local and far forward care (5), clothing issues and protection from injury, continuous renal replacement therapy (4), antibiotic use (8), wound excision and closure techniques, diagnosis and treatment of head injury including blast injury (28), pharmacokinetics of antibiotics in the severely injured, topical wound treatments including silver products and vacuum assisted wound closure, wound healing of the skin donor site, hemorrhage control in the burn OR, nutrition during ICU stay and during outpatient recuperation, temperature control in the burned patient, hypotension control strategies, and heterotopic ossification in the severely burned. Critical advances in burn care and trauma care including some listed above developed and tested at the USAISR have significantly improved patient survival and outcomes in combat casualties.

9.0 THE FUTURE OF RESEARCH AT THE USAISR

The unique relationship between clinical care and research has resulted in an initiative to centralize combat casualty care research at Ft. Sam Houston with the USAISR and Brooke Army Medical Center (BAMC). This realignment will be realized within the next year and will bring additional research areas to the USAISR/BAMC campus to leverage these capabilities. Future opportunities in dental research, blood research, and eye trauma are all examples of this expanded research mission. In order to execute this expanded mission, construction projects are underway to double the laboratory space available, and relocate or hire over 150 research personnel in these mission areas. This expanded scope comes with expanded collaboration, as the new research facility will house not only Army researchers, but also U.S. Navy and U.S. Air Force as well. The future of combat casualty care is joint, coordinated between the U.S. military services and with our international partners to speed innovation and provide world class care to combat casualties.

- [1] Batchinsky AI, Cancio LC, Salinas J, Kuusela T, Cooke WH, Wang JJ, Boehme M, Convertino VA, and Holcomb JB. Prehospital loss of R-to-R interval complexity is associated with mortality in trauma patients. *J Trauma* 63: 512-518, 2007.
- [2] Blackbourne LH. Combat damage control surgery. *Crit Care Med* 36: S304-310, 2008.
- [3] Brohi K. Diagnosis and management of coagulopathy after major trauma. *Br J Surg* 96: 963-964, 2009.
- [4] Chung KK, Lundy JB, Matson JR, Renz EM, White CE, King BT, Barillo DJ, Jones JA, Cancio LC, Blackbourne LH, and Wolf SE. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. *Crit Care* 13: R62, 2009.
- [5] Chung KK, Wolf SE, Cancio LC, Alvarado R, Jones JA, McCorcle J, King BT, Barillo DJ, Renz EM, and Blackbourne LH. Resuscitation of severely burned military casualties: fluid begets more fluid. *J Trauma* 67: 231-237; discussion 237, 2009.
- [6] Convertino VA, Ryan KL, Rickards CA, Salinas J, McManus JG, Cooke WH, and Holcomb JB. Physiological and medical monitoring for en route care of combat casualties. *J Trauma* 64: S342-353, 2008.

- [7] Cooke WH, Rickards CA, Ryan KL, and Convertino VA. Autonomic compensation to simulated hemorrhage monitored with heart period variability. *Crit Care Med* 36: 1892-1899, 2008.
- [8] D'Avignon LC, Saffle JR, Chung KK, and Cancio LC. Prevention and management of infections associated with burns in the combat casualty. *J Trauma* 64: S277-286, 2008.
- [9] Dubick MA, Brooks DE, Macaitis JM, Bice TG, Moreau AR, and Holcomb JB. Evaluation of commercially available fluid-warming devices for use in forward surgical and combat areas. *Mil Med* 170: 76-82, 2005.
- [10] Gaylord KM, Cooper DB, Mercado JM, Kennedy JE, Yoder LH, and Holcomb JB. Incidence of posttraumatic stress disorder and mild traumatic brain injury in burned service members: preliminary report. *J Trauma* 64: S200-205; discussion S205-206, 2008.
- [11] Grathwohl KW, Venticinque SG, Blackburne LH, and Jenkins DH. The evolution of military trauma and critical care medicine: applications for civilian medical care systems. *Crit Care Med* 36: S253-254, 2008.
- [12] Holcomb JB, McMullin NR, Pearse L, Caruso J, Wade CE, Oetjen-Gerdes L, Champion HR, Lawnick M, Farr W, Rodriguez S, and Butler FK. Causes of death in U.S. Special Operations Forces in the global war on terrorism: 2001-2004. *Ann Surg* 245: 986-991, 2007.
- [13] Kauvar DS, and Baer DG. Effect of a targeted education intervention on the incidence of waste-burning injuries in a military population. *J Burn Care Res* 30: 700-704, 2009.
- [14] Kelly JF, Ritenour AE, McLaughlin DF, Bagg KA, Apodaca AN, Mallak CT, Pearse L, Lawnick MM, Champion HR, Wade CE, and Holcomb JB. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *J Trauma* 64: S21-26; discussion S26-27, 2008.
- [15] Kheirabadi BS, Edens JW, Terrazas IB, Estep JS, Klemcke HG, Dubick MA, and Holcomb JB. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. *J Trauma* 66: 316-326; discussion 327-318, 2009.
- [16] Kheirabadi BS, Scherer MR, Estep JS, Dubick MA, and Holcomb JB. Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. *J Trauma* 67: 450-459; discussion 459-460, 2009.
- [17] Kheirabadi BS, Sieber J, Bukhari T, Rudnicka K, Murcin LA, and Tuthill D. High-pressure fibrin sealant foam: an effective hemostatic agent for treating severe parenchymal hemorrhage. *J Surg Res* 144: 145-150, 2008.
- [18] Klemcke HG, Baer DG, Pankratz VS, Cox A, Cortez DS, Garrett MR, Joe B, and Ryan KL. Is survival time after hemorrhage a heritable, quantitative trait?: an initial assessment. *Shock* 29: 748-753, 2008.
- [19] Lee J, Kim JG, Mahon S, Tromberg BJ, Ryan KL, Convertino VA, Rickards CA, Osann K, and Brenner M. Tissue hemoglobin monitoring of progressive central hypovolemia in humans using broadband diffuse optical spectroscopy. *J Biomed Opt* 13: 064027, 2008.

- [20] Masini BD, Waterman SM, Wenke JC, Owens BD, Hsu JR, and Ficke JR. Resource utilization and disability outcome assessment of combat casualties from Operation Iraqi Freedom and Operation Enduring Freedom. *J Orthop Trauma* 23: 261-266, 2009.
- [21] McGhee LL, Maani CV, Garza TH, DeSocio PA, Gaylord KM, and Black IH. The relationship of intravenous midazolam and posttraumatic stress disorder development in burned soldiers. *J Trauma* 66: S186-190, 2009.
- [22] McGhee LL, Maani CV, Garza TH, Gaylord KM, and Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma* 64: S195-198; Discussion S197-198, 2008.
- [23] Owens BD, Kragh JF, Jr., Macaitis J, Svoboda SJ, and Wenke JC. Characterization of extremity wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *J Orthop Trauma* 21: 254-257, 2007.
- [24] Owens BD, Kragh JF, Jr., Wenke JC, Macaitis J, Wade CE, and Holcomb JB. Combat wounds in operation Iraqi Freedom and operation Enduring Freedom. *J Trauma* 64: 295-299, 2008.
- [25] Owens BD, White DW, and Wenke JC. Comparison of irrigation solutions and devices in a contaminated musculoskeletal wound survival model. *J Bone Joint Surg Am* 91: 92-98, 2009.
- [26] Park MS, Salinas J, Wade CE, Wang J, Martini W, Pusateri AE, Merrill GA, Chung K, Wolf SE, and Holcomb JB. Combining early coagulation and inflammatory status improves prediction of mortality in burned and nonburned trauma patients. *J Trauma* 64: S188-194, 2008.
- [27] Rickards CA, Ryan KL, Cooke WH, Romero SA, and Convertino VA. Combat stress or hemorrhage? Evidence for a decision-assist algorithm for remote triage. *Aviat Space Environ Med* 79: 670-676, 2008.
- [28] Ritenour AE, and Baskin TW. Primary blast injury: update on diagnosis and treatment. *Crit Care Med* 36: S311-317, 2008.
- [29] Ryan KL, Cooke WH, Rickards CA, Lurie KG, and Convertino VA. Breathing through an inspiratory threshold device improves stroke volume during central hypovolemia in humans. *J Appl Physiol* 104: 1402-1409, 2008.
- [30] Salinas J, Drew G, Gallagher J, Cancio LC, Wolf SE, Wade CE, Holcomb JB, Herndon DN, and Kramer GC. Closed-loop and decision-assist resuscitation of burn patients. *J Trauma* 64: S321-332, 2008.
- [31] Sharar SR, Miller W, Teeley A, Soltani M, Hoffman HG, Jensen MP, and Patterson DR. Applications of virtual reality for pain management in burn-injured patients. *Expert Rev Neurother* 8: 1667-1674, 2008.
- [32] Soller BR, Ryan KL, Rickards CA, Cooke WH, Yang Y, Soyemi OO, Crookes BA, Heard SO, and Convertino VA. Oxygen saturation determined from deep muscle, not thenar tissue, is an early indicator of central hypovolemia in humans. *Crit Care Med* 36: 176-182, 2008.
- [33] Soller BR, Yang Y, Soyemi OO, Ryan KL, Rickards CA, Walz JM, Heard SO, and Convertino VA. Noninvasively determined muscle oxygen saturation is an early indicator of central hypovolemia in humans. *J Appl Physiol* 104: 475-481, 2008.



- [34] Svoboda SJ, Owens BD, Gooden HA, Melvin ML, Baer DG, and Wenke JC. Irrigation with potable water versus normal saline in a contaminated musculoskeletal wound model. *J Trauma* 64: 1357-1359, 2008.

- [35] Wolf SE, Kauvar DS, Wade CE, Cancio LC, Renz EP, Horvath EE, White CE, Park MS, Wanek S, Albrecht MA, Blackburne LH, Barillo DJ, and Holcomb JB. Comparison between civilian burns and combat burns from Operation Iraqi Freedom and Operation Enduring Freedom. *Ann Surg* 243: 786-792; discussion 792-785, 2006.